The effect of emphysema on survival in patients with idiopathic pulmonary fibrosis: A retrospective study in Taiwan

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Abstract

Background: Idiopathic pulmonary fibrosis (IPF) is a rare and chronic fibrosing interstitial lung disease. However, the clinical features and outcomes of IPF in Taiwan have not been well studied. In addition, the survival difference between patients with IPF alone and combined pulmonary fibrosis and emphysema (CPFE) remains controversial.

Methods: Patients diagnosed with IPF between 2006 and 2016 were retrospectively enrolled in this study. IPF was defined according to the 2011 American Thoracic Society/European Respiratory Society guideline. The clinical features, comorbidities, and outcomes of CPFE group and IPF-alone group were compared. The extents of emphysema and fibrosis were evaluated.

Results: In total, 114 patients with IPF were enrolled, and 86.8% of them were men with a mean age of 77.8 years. The median survival was 3.33 years in all patients with IPF. Moreover, 30 patients (26.3%) met the CPFE criteria. The CPFE group had a higher percentage of smokers (90% vs 50%, $p < 0.001$), higher forced vital capacity (82% vs 59%, $p < 0.001$), and lower fibrosis scores (8.5 ± 2.9 vs 10 ± 3.2, $p = 0.022$) than did the IPF-alone group. The baseline room air saturation and percentage of pulmonary hypertension were similar between the two groups. The survival time was not significantly different between the CPFE and IPF-alone groups (median survival, 3.58 vs 2.39 years, $p = 0.163$). In the multivariate analysis, higher fibrosis score, room air saturation < 90%, and lung cancer were significant factors associated with mortality.

Conclusion: Our study showed that emphysema had no significant effect on the survival of patients with IPF. The outcome of IPF was mainly determined by the baseline disease severity and other comorbidities.

Keywords: Combined pulmonary fibrosis and emphysema; Idiopathic pulmonary fibrosis; Interstitial lung disease; Usual interstitial pneumonia

1. INTRODUCTION

Idiopathic pulmonary fibrosis (IPF) is a rare, chronic, and progressive fibrosing interstitial lung disease (ILD) of unknown etiology. IPF is the most common entity among idiopathic interstitial pneumonia and has the worst prognosis.[1,2] Moreover, progression to hypoxic respiratory failure is inevitable, and the clinical course is unpredictable and variable.[1] There have been no effective treatments until recently, when two novel medications were proven to effectively delay lung function decline and likely prolong overall survival.[2–4] IPF is associated with characteristic radiological and histopathological patterns of usual interstitial pneumonia (UIP).[5] Recent studies on IPF reported a median survival of 3.5 to 4.4 years in the United States,[6–8] 3.7 years in Finland,[9] and 2.9 to 3.8 years in Asia.[10–13]

Taiwan is an Asian country to the east of China, with a population of 23.4 million. More than 95% of the population is Chinese, and the culture is similar to that of China.[14] However, IPF data in Taiwan are limited. Only one previous study by Lai et al (n = 789) analyzing the Taiwan National Health Insurance (NHI) database showed an extraordinarily short median survival of 0.7 to 0.9 years.[15] In this NHI study, the cohort comprised 2,619,534 patients, representing 10% of the general population in Taiwan, and the patients with IPF were enrolled from 1997 to 2007.[15]

In addition, combined pulmonary fibrosis and emphysema (CPFE) has been found to be a distinct entity with clinical features different from those of IPF alone. Emphysema was found in 8% to 51% of patients with IPF via high-resolution computed tomography (HRCT), whereas pulmonary fibrosis was found in 4.4% to 8% of patients with emphysema.[16] Although it was traditionally believed that CPFE had a significantly poorer prognosis than did IPF alone, previous studies evaluated heterogeneous patient populations, used variable definitions of CPFE, and conducted inadequate evaluation of potential confounding factors. Moreover, the survival time of patients with CPFE still remains controversial.[16–18]

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Therefore, the purpose of this study was to compare the outcome of patients with IPF who had emphysema with that of patients without emphysema. The survival time was the primary endpoint of this study. The secondary endpoints were the factors associated with IPF mortality.

2. METHODS

2.1. Subjects

This was a retrospective cohort study based on medical records and radiological reports maintained at a 1455-bed tertiary medical center in southern Taiwan. During the period between January 1, 2006, and December 31, 2016, patients with HRCT reports suggesting UIP or medical records indicating suspected IPF were retrospectively collected. These target patients were selected from the electronic medical chart system in our hospital, by searching for the keywords: idiopathic pulmonary fibrosis, IPF, usual interstitial pneumonia, and UIP. This study was approved by the Institutional Review Board of our hospital, which waived the requirement for informed consent (VGHKS16-CT12-03).

2.2. Case definition

IPF was defined using the diagnostic criteria of the 2011 American Thoracic Society/European Respiratory Society guideline. The HRCT UIP pattern is defined as reticular opacities and honeycombing, with subpleural and basal predominance, and without any features that are inconsistent with the UIP pattern.[5] A definite UIP pattern on HRCT without other known causes of ILD, such as environmental exposure, connective tissue disease (CTD), and drug toxicity, allows the diagnosis of IPF to be made without the need for surgical lung biopsy.[5] CPFE is defined as IPF coexisting with pulmonary emphysema on the basis of HRCT findings.

2.3. HRCT evaluation

On HRCT, emphysema is defined as well-demarcated areas of decreased attenuation compared to the contiguous normal lung and with a very thin (<1 mm) or absent wall, with or without multiple bullae (>1 cm in diameter). Fibrosis is defined as lesions of reticular opacity and honeycombing.[19] The extent of pulmonary fibrosis and emphysema was determined by Dr. Chiu-Fan Chen and by using visual estimation of the fibrosis score and emphysema score.

The lungs were divided into six zones (the upper, middle, and lower zones in both the lungs), and each zone was evaluated separately. The upper zone was defined as the region above the level of the tracheal carina, the lower zone as the region below the level of the inferior pulmonary vein, and the middle zone as the region between the upper and lower zones. The extent of emphysema and fibrosis in each lung zone was determined using semiquantitative scores: score 0, none; score 0.5, <5%; score 1, 5% to 24%; score 2, 25% to 49%; score 3, 50% to 74%; and score 4, ≥75%. The total emphysema score was the sum of scores of six lung zones, and so was total fibrosis score. A clinically significant pulmonary emphysema was defined as that with a total emphysema score > 3.[19,20] Pulmonary hypertension (PH) was defined as a pulmonary trunk size ≥ 29 mm on computed tomography (CT). The pulmonary trunk size was measured at the level of its bifurcation, perpendicular to the long axis.[21]

2.4. Data collection

For each patient with IPF, the baseline clinical features such as demographic data, smoking status, room air oxygen saturation, forced vital capacity (FVC), diffusing capacity for carbon monoxide (DLCO), comorbidities, and medications were collected. The primary endpoint was the survival time, and the secondary endpoints were the factors associated with IPF mortality. Survival time was calculated from the date of the first HRCT diagnosis to the date of the last follow-up. The medical records of each patient were reviewed up to March 31, 2019. The file containing the patients' clinical and imaging data was protected by a password. The name and medical record number of each patient were removed, and a patient code was assigned instead. The information linking each patient's code to the corresponding medical record number was saved in another computer and was also protected by a password. Only Chiu-Fan Chen and Ruay-Sheng Lai could access these files.

2.5. Statistical analyses

Continuous variables (age, body mass index, FVC, DLCO, total fibrosis score, total emphysema score, and pulmonary trunk size) were evaluated for normal distribution using the Shapiro–Wilk test and histograms. Normally distributed continuous variables were expressed as mean ± standard deviation and were compared using independent *t* tests. Non-normally distributed variables were expressed as medians and interquartile range (IQR) and comapred using Mann-Whitney U tests. Categorical variables were expressed as number (percentage) and were compared using the chi-squared tests or using Fisher's exact tests if the expected count in any cell was <5. Survival analysis was performed using the Kaplan–Meier method. Log-rank test was used to evaluate survival difference. Cox regression analysis was used to analyze the prognostic factors of patients with IPF. Factors with p values <0.1 in the univariate analysis were entered into the multivariate analysis. Statistical analysis was conducted using IBM SPSS Statistics for Windows, Version 20.0 (IBM Corp., Armonk, NY, USA). Two-tailed p values < 0.05 were considered statistically significant.

3. RESULTS

3.1. Baseline characteristics

Initially, 213 patients were included for analysis, and 125 were classified as having definite UIP, 22 as having possible UIP, and 66 as having HRCT features inconsistent with UIP (Fig. 1).

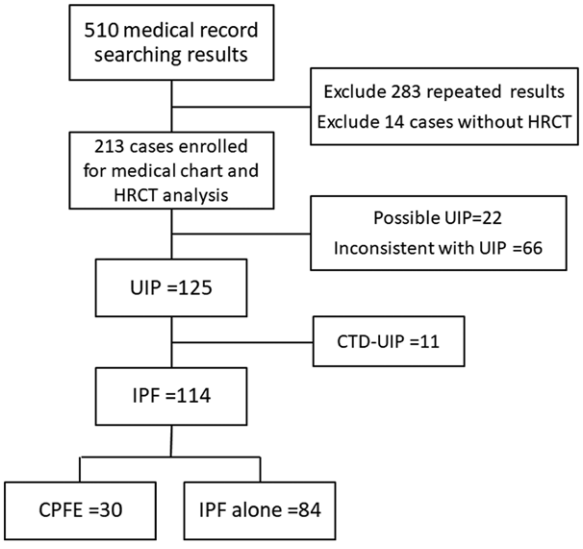

Fig. 1 Flowchart illustrating the selection of IPF cases. CPFE, combined pulmonary fibrosis and emphysema; CTD, connective tissue disease; HRCT, high-resolution computed tomography; IPF, idiopathic pulmonary fibrosis; UIP, usual interstitial pneumonia.

Among the 125 patients with definite UIP, 11 with associated CTD were excluded. The remaining 114 patients were classified as having IPF, with all showing typical honeycombing and reticular opacities on HRCT. Thirty of the 114 patients with IPF (26.3%) met the CPFE criteria. The baseline clinical features, pulmonary functions, and fibrosis extents of all patients with IPF are summarized in Table 1.

The mean age of the patients with IPF was 77.8 ± 9.4 years, the median age was 80 years (IQR 74-84), and there was a male predominance (86.8%). The youngest patient was 43 years old at diagnosis, and the oldest was 97 years old. Only one patient was younger than 50 years of age. Among the patients, 60.5% were smokers. The median %FVC of predicted was 70.5% (IQR 50.5-84, n = 78) and the median %DLCO of predicted was 35% (IQR 25.5-53.3, n = 30). Room air resting saturation measured using pulse oximeter revealed that 64.5% of patients had saturation ≥95% at diagnosis. The comparison of the clinical features of CPFE and IPF alone is shown in Table 1. The CPFE group had a significantly higher smoking rate (90% vs 50%, $p < 0.001$), higher %FVC of predict (82% vs 59%, $p < 0.001$), and lower total fibrosis score (8.5 ± 2.9 vs 10 ± 3.2, $p = 0.022$) than did the IPF-alone group. The baseline room air saturation, lung cancer, and PH were similar between the two groups. The baseline comorbidities of the patients with IPF are also summarized in Table 1. The three most common comorbidities were PH, hypertension, and chronic obstructive pulmonary disease. The data regarding steroid (including inhaled corticosteroid) and *N*-acetylcysteine use for ≧28 days are presented in Table 1. There was no difference in the medication use between the CPFE and IPF-alone groups.

3.2. Survival time

The IPF survival outcomes are shown in Table 1. The Kaplan–Meier curves of overall survival are shown in Fig. 2A. The median survival was 3.33 years in all patients with IPF, with the longest survival being up to 14.3 years. Fig. 2B shows the survival curve of the CPFE and IPF-alone groups. No significant survival difference was observed between the groups (median survival, 3.58 vs 2.39 years; log-rank test $p = 0.163$).

Table 1

Clinical characteristics and outcomes of patients in the CPFE and IPF-alone groups

	All IPF (n = 114)	CPFE (n = 30)	IPF alone (n = 84)	*p*
Age, y (IQR)	80 (74-84)	79.5 (73.5-84)	80 (74-84.8)	0.730
Male, n (%)	99 (86.8)	28 (93.3)	71 (84.5)	0.347
BMI kg/m_2	23.7 ± 3.7	23.7 ± 4	23.6 ± 3.7	0.906
Smoking, n (%)	69 (60.5)	27 (90)	42 (50)	<0.001*
Room air SpO_2, n (%)				0.510
≧95%	71 (64.5)	21 (72.4)	50 (61.7)	
90%-94%	16 (14.5)	4 (13.8)	12 (14.8)	
<90%	23 (21)	4 (13.8)	19 (23.5)	
%FVC[a], % (IQR)	70.5 (50.5-84)	82 (72-91)	59 (47-80)	<0.001*
%DLCO[a], % (IQR)	35 (25.5-53.3)	32 (22.5-55.8)	36.5 (26.2-53.3)	0.622
Total fibrosis score	9.6 ± 3.2	8.5 ± 2.9	10 ± 3.2	0.022*
Total emphysema score (IQR)	0 (0-4)	6.5 (4.8-9.6)	0 (0-1)	<0.001*
Pulmonary trunk size, mm (IQR)	29.3 (26.8-32.5)	28.1 (25.2-31.6)	29.4 (27-32.9)	0.137
Comorbidity, n (%)				
Pulmonary HTN	63 (55.3)	14 (46.7)	49 (58.3)	0.270
Hypertension	61 (53.5)	15 (50)	46 (54.8)	0.654
COPD[b]	38 (33.3)	30 (100)	8 (9.5)	<0.001*
Heart failure	23 (20.2)	6 (20)	17 (20.2)	0.978
Diabetes mellitus	21 (18.4)	3 (10)	18 (21.4)	0.166
Coronary artery disease	21 (18.4)	6 (20)	15 (17.9)	0.795
Other cancer	19 (16.7)	3 (10)	16 (19)	0.254
Chronic kidney disease	17 (14.9)	4 (13.3)	11 (13.1)	1.000
Stroke	13 (11.4)	4 (13.3)	9 (10.7)	0.741
Lung cancer	11 (9.6)	5 (16.7)	6 (7.1)	0.154
GERD	7 (6.1)	4 (13.3)	3 (3.6)	0.077
Medication, n (%)				
Steroid/ICS >28 d	43 (37.7)	11 (36.7)	32 (38.1)	0.890
NAC >28 d	41 (36)	12 (40)	29 (34.5)	0.592
Outcomes				
Median survival, y	3.33	3.58	2.39	0.163[c]
1-y survival	73.1%	76.9%	72%	
2-y survival	59.6%	72.1%	54.8%	
5-y survival	37.5%	44.9%	35.7%	

Data are presented as mean ± SD or median (IQR) for continuous variables, and n (%) for categorical variables. *$p < 0.05$.

[a]The FVC and DLCO data were obtained using a pulmonary function test within 1 y of IPF diagnosis. FVC data: n = 78 (CPFE: 23, IPF alone: 55), DLCO data: n = 30 (CPFE: 8, IPF alone: 22).

[b]COPD is defined on the basis of the clinical history, a pulmonary function test showing FEV1/FVC < 70%, or CT evidence of emphysema.

[c]Log-rank test *p* value.

BMI = body mass index; COPD = chronic obstructive pulmonary disease; CPFE = combined pulmonary fibrosis and emphysema; CT = computed tomography; DLCO = diffusing capacity for carbon monoxide; FEV1 = forced expiratory volume in one second; FVC = forced vital capacity; GERD = gastroesophageal reflux disease; HTN = hypertension; ICS = inhaled corticosteroid; IQR = interquartile range; IPF = idiopathic pulmonary fibrosis; NAC = *N*-acetylcysteine; SD = standard deviation; SpO_2 = peripheral oxygen saturation.

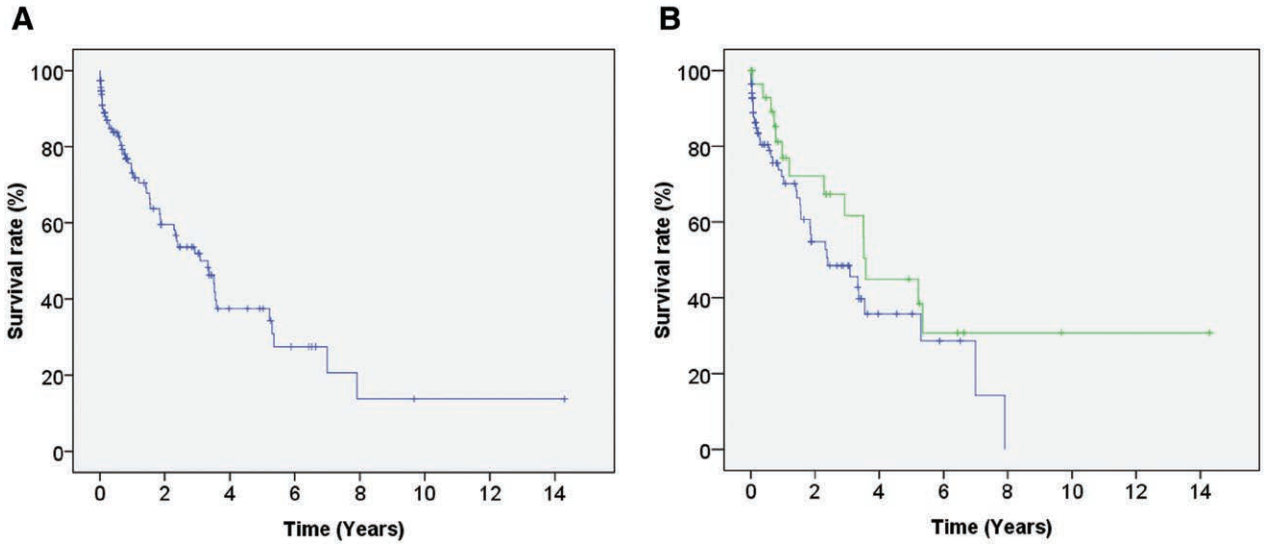

Fig. 2 The IPF survival curves. (A) Kaplan–Meier survival curve of all patients with IPF. The median survival was 3.33 years. (B) Kaplan–Meier survival curve of CPFE (green) and IPF alone (blue) groups. The median survival was 3.58 y in the CPFE group and 2.39 y in the IPF alone group; log-rank test $p = 0.163$. CPFE, combined pulmonary fibrosis and emphysema; IPF, idiopathic pulmonary fibrosis.

3.3. Prognostic factors

The prognostic factor analysis is shown in Table 2. Univariate Cox regression revealed that the significant factors associated with higher mortality in patients with IPF were PH, lung cancer, total fibrosis score, and initial room air saturation < 90%. However, emphysema showed no significant association with the survival of patients with IPF. In multivariate Cox regression, the significant prognostic factors were total fibrosis score (hazard ratio [HR] = 1.140, $p = 0.004$), lung cancer (HR = 4.637, $p = 0.001$), and initial room air saturation < 90% (HR = 5.433, $p < 0.001$).

4. DISCUSSION

Our study demonstrated that the survival of patients with IPF in Taiwan is comparable to that of patients in the Western or other Asian countries, in contrast to the extremely short survival time reported in a previous NHI database study in Taiwan.[15] CPFE was associated with more smoking, higher FVC, and lower fibrosis score. The survival was not significantly different between the CPFE and IPF-alone groups in our study. PH, room air oxygen saturation, and lung cancer were also not significantly different between the two groups. The baseline CT fibrosis score, lung

Table 2

Factors associated with mortality in patients with IPF (n = 114)

	Univariate analysis			Multivariate analysis		
Factors	**HR**	**95% CI**	***p***	**HR**	**95% CI**	***p***
Gender (male)	0.857	0.402-1.829	0.690			
Age	1.004	0.974-1.035	0.795			
Smoking	0.856	0.490-1.498	0.587			
Emphysema	0.644	0.346-1.200	0.166			
Pulmonary HTN	1.810	1.039-3.154	0.036*	1.528	0.804-2.902	0.196
Hypertension	0.761	0.443-1.310	0.325			
COPD	0.772	0.431-1.384	0.385			
Heart failure	1.869	0.994-3.512	0.052	1.227	0.574-2.620	0.598
Diabetes mellitus	1.476	0.730-2.986	0.279			
CAD	1.250	0.654-2.389	0.499			
Other cancer	1.218	0.569-2.604	0.612			
CKD	1.479	0.759-2.883	0.250			
Stroke	1.059	0.473-2.370	0.888			
Lung cancer	2.670	1.295-5.505	0.008*	4.637	1.844-10.343	0.001*
GERD	2.833	0.999-8.034	0.050	2.083	0.645-6.732	0.220
SpO_2 (room air)						
≥95%	1			1		
90%-94%	1.567	0.712-3.449	0.264	1.791	0.785-4.088	0.166
<90%	6.222	2.768-13.989	<0.001*	5.433	2.307-12.796	<0.001*
Total fibrosis score	1.132	1.048-1.223	0.002*	1.140	1.042-1.246	0.004*
Total emphysema score	0.941	0.860-1.029	0.184			

*$p < 0.05$.

CAD = coronary artery disease; CI = confidence interval; CKD = chronic kidney disease; COPD = chronic obstructive pulmonary disease; GERD = gastroesophageal reflux disease; HR = hazard ratio; HTN = hypertension; IPF = idiopathic pulmonary fibrosis; SpO_2 = peripheral oxygen saturation.

cancer, and room air saturation < 90% were independent factors associated with IPF mortality.

The median survival of patients with IPF was 3.33 years in our study. Our result demonstrates that the median survival of patients with IPF in Taiwan is comparable to that of patients in the United States, Finland, and other Asian countries, which ranges from 3 to 4 years.[6–13] Regarding the previous Taiwan IPF NHI study by Lai et al, which showed a median survival of only 0.7 to 0.9 years,[15] the dramatic difference is probably due to the disease coding based on the International Classification of Diseases, Ninth Revision (ICD-9), underdiagnosis, and delayed diagnosis. In that study, the IPF prevalence and incidence rates were lower than those of other countries.[2,9,10,15] In addition, the incidence rate of IPF had a sixfold increase from 1997 to 2007, which is obviously unreasonable. It is very likely that there had been considerable IPF underdiagnoses, particularly during the early study period, which may have been due to inaccurate ICD-9 coding and physician's misdiagnosis.[15] The NHI study data included patients from medical centers, regional hospitals and local hospitals. Local hospitals are also possible sources of underdiagnosis and delayed diagnosis, because of the inadequate experience in IPF diagnosis and ICD-9 coding. Furthermore, the Kaplan–Meier curves for IPF survival in the NHI study showed a median survival of approximately 4 years, in contrast to 0.7 to 0.9 years presented in its own conclusion.[15] The author did not explain the inconsistency of these study results; therefore, the conclusion of the NHI study is questionable.

The mean diagnosis age of 77.8 years in our patients with IPF was older than that in other countries (60.3-73.5 years),[6–13] and up to 48% of patients with IPF in our study were diagnosed between the ages of 80 to 89 years. Further, 86.8% of patients in our study were men, and this percentage was also higher than that observed in IPF studies in other countries (ranging between 59% and 85.7%).[6–13] Smoking history was present in 60.5% of the patients in our study, and the smoking percentage in IPF was significantly higher than the mean adult smoking rate in Taiwan (35.6% for men and 4.3% for women, data from 2005 to 2014).[22]

CPFE is defined as the coexistence of upper lobe emphysema and lower lobe predominant pulmonary fibrosis (mainly IPF/UIP). According to this original definition, CPFE is a heterogeneous syndrome.[16,17] Although the majority of pulmonary fibrosis is IPF, some cases of nonspecific interstitial pneumonias, CTD–ILD, and drug-induced ILD may be included and may result in a heterogeneous study population and outcome. Cottin et al first described the syndrome of CPFE in 2005, and only 51% of the cases were typical IPF. In his study, the median survival of patients with CPFE reached 6.1 years, and 47% of the patients had PH.[23] Mitchell et al had demonstrated that IPF with emphysema showed more severe radiographic fibrosis and emphysema than did non-IPF UIP with emphysema, and this was not explained by the confounding factors.[24] Therefore, it was suggested that IPF with emphysema is a distinct disease entity, and studies should focus on this patient population to improve the quality of clinical analysis.[24]

After a decade of clinical research, it still remains controversial whether emphysema contributes to a worse prognosis in IPF.[16–18] A literature summary of studies comparing CPFE and IPF is shown in Table 3.[13,19,25–30] Four of the studies showed worse survival in CPFE than in IPF alone,[19,25–27] three showed similar survival,[13,28,30] and one showed better survival in CPFE than in IPF alone.[29] The severity of fibrosis, coexistence of PH, and lung cancer are three important prognostic factors of IPF in our study. Cottin et al had recommended controlling important confounding factors when evaluating the survival difference between CPFE and IPF alone.[31] They also suggested that CPFE was associated with PH and, therefore, contributed to a poorer prognosis in CPFE.[18,23]

In our literature review, only five studies on CPFE evaluated both the fibrosis score and PH.[19,25,26,28,30] Mejía et al revealed more PH (90% vs 58%, $p < 0.001$) and higher fibrosis score ($p = 0.015$) in CPFE than in IPF, which probably contributed to the worse prognosis of CPFE. Emphysema was not a significant prognostic factor.[25] Sugino et al demonstrated a similar estimated pulmonary artery systolic pressure (ePASP) (30.8 vs

Table 3

Literature review on the survival of patients with CPFE and those with IPF alone

Reference	CPFE vs IPF	Median survival	Comment
Worse survival			
Mejía et al,[25] Mexico[a]	n =31 and 79	2.08 vs 2.83 y, $p = 0.01$	Lung biopsy rate, 38%. Higher rate of PH in CPFE than in IPF (90% vs 58%, $p < 0.001$) and higher fibrosis score in CPFE ($p = 0.015$). No lung cancer data.
Sugino et al,[26] Japan	n = 46 and 62	1.83 vs 4.17 y, $p = 0.01$	Similar ePASP (30.8 vs 30.9 mmHg). Slightly lower fibrosis score in CPFE ($p < 0.001$). Much higher lung cancer rate in CPFE (50% vs 14.5%, $p < 0.001$).
Zhang et al,[27] China	n = 87 and 105	5-y survival: 43.4% vs 65.6%, $p < 0.05$	Similar PH (44.8% vs 42.9%) and lung cancer rates (9.2% vs 7.6%). Fibrosis score not shown. PH was mortality predictor.
Kohashi et al,[19] Japan	n = 8 and 39	4.75 vs 6.08 y, $p = 0.007$	All cases were surgical biopsy proven. Similar PH rates (20% vs 22.2%) and fibrosis scores. None had lung cancer at baseline. Emphysema was a factor of poor prognosis in the multivariate analysis.
Similar survival			
Ryerson et al,[28] USA	n = 29 and 336	2.8 vs 2.8 y, $p = 0.5$	Higher ePASP in the CPFE group (56.6 vs 39.6 mmHg, $p = 0.008$). Lower fibrosis scores in CPFE ($p = 0.003$). No lung cancer data.
Ma et al,[13] China	n = 23 and 33	3.33 vs 3.17 y, $p = 0.79$	No data on PH, lung cancer, or fibrosis score.
Jacob et al,[30] UK	n = 105 and 167	2.67 vs 3.04 y[b], $p = 0.20$	ILD extent was a mortality predictor. Similar PH rates in both groups. Higher lung cancer rate in the CPFE group (9.5% vs 1.2%, $p = 0.001$).
Present study, 2019, Taiwan	n = 30 and 84	3.58 vs 2.39 y, $p = 0.163$	Fibrosis score was lower in CPFE than in IPF ($p = 0.022$). Similar PH (46.7% vs 58.3%, $p = 0.27$) and lung cancer rates (16.7% vs 7.1%, $p = 0.154$) in both groups.
Better survival			
Kurashima et al,[29] Japan	n = 129 and 233	8.5 vs 7.5 y, $p = 0.047$	Very long survival in this study. Similar fibrosis severity between the two groups. No PH data. Patients with lung cancer at baseline were excluded.

[a]Emphysema became an insignificant factor in the multivariate analysis. The worse prognosis of CPFE was associated with severe PH.

[b]Restricted mean survival rather than median survival was used in this study.

CPFE = combined pulmonary fibrosis and emphysema; ePASP = estimated pulmonary artery systolic pressure; ILD = interstitial lung disease; IPF = idiopathic pulmonary fibrosis; PH = pulmonary hypertension.

30.9 mmHg) in CPFE and IPF, but showed a slightly lower fibrosis score ($p < 0.001$) and a much higher lung cancer rate (50% vs 14.5%, $p < 0.001$) in CPFE than in IPF. Emphysema was not a significant prognostic factor, and the worse survival rate of patients with CPFE might be because of the very high lung cancer rate in CPFE.[26] Kohashi et al conducted a study on biopsy-proven CPFE, with similar PH (20% vs 22.2%) and fibrosis scores, and showed worse survival in CPFE than in IPF. Lung cancer was absent at baseline in both groups. Emphysema was a significant poor prognostic factor in multivariate analysis. However, in their study, the PH data were only available in 68% of the patients.[19] Ryerson et al revealed a higher ePASP (56.6 vs 39.6 mmHg, $p = 0.008$) and lower fibrosis score ($p = 0.003$) in CPFE than in IPF, and the survival rate was similar in the two groups.[28] In the latest study by Jacob et al, emphysema was also not a prognostic factor and was not associated with more PH. Lower fibrosis extent ($p = 0.02$) and higher lung cancer rate (9.5% vs 1.2%, $p = 0.001$) were noted in the study.[30,32]

As for the present study, although the difference in PH (46.7% vs 58.3%) and lung cancer rate (16.7% vs 7.1%) were not significant, a significantly lower fibrosis score was observed in CPFE than in IPF ($p = 0.022$), and this may account for the non-significant trend of higher survival rate of patients with CPFE in this study. Taken together with the findings of previous studies, our findings suggest that emphysema is not an independent prognostic factor in IPF.[19,25,26,28,30,32] The survival of patients with IPF is more likely determined by the baseline disease severity and other comorbidities.

Our study has several limitations. This was a single-center retrospective study; therefore, some pulmonary function results were incomplete. The survival might have been underestimated for those patients with IPF who were transferred from other local hospitals. Some patients were lost to follow up, and the end result was not obtained. The loss follow-up rate was 27.2% within 1 year (31/114), and 39.5% (45/114) within 5 years. Moreover, our study included only patients with IPF with a UIP pattern on HRCT, but not those with an atypical HRCT pattern. Therefore, our study results cannot predict the survival of patients with IPF without a typical UIP pattern on HRCT.

To our knowledge, this is the first study on IPF in Taiwan that involved a comprehensive review of HRCT imaging and medical information. All patients with IPF in our study had a definite UIP pattern on HRCT. A definite UIP pattern on HRCT has more than 90% positive predictive value for the histological UIP pattern, and thus, surgical lung biopsy is not necessary.[5] Therefore, the IPF diagnosis in our study is reliable. In conclusion, the survival of patients with IPF is mainly determined by the baseline comorbidities and disease severity. We found that emphysema has no significant prognostic effect on IPF. The inconsistent CPFE outcomes between different studies are probably due to the heterogeneous patient populations.

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